Attorney Docket No. 033072-022

CLAIMS

What Is Claimed Is:

1. An isolated modified GPCR or biologically active fragment thereof comprising a DRY motif, wherein the DRY motif is modified to contain an amino acid other than arginine at position 2, and wherein the modified GPCR or biologically active fragment thereof is constitutively desensitized in absence of agonist.

2. The isolated modified GPCR of claim 1, wherein the isolated and modified GPCR binds arrestin, localizes to clathrin-coated pits, or localizes in endocytic vesicles or endosomes in absence of agonist.

3. The isolated modified GPCR of claim 1, wherein the isolated and modified GPCR binds arrestin in absence of agonist.

4. The isolated modified GPCR of claim 1, wherein the isolated and modified GPCR localizes in endocytic vesicles or endosomes in absence of agonist.

5. The isolated modified GPCR of claim 1, wherein the isolated, modified GPCR is derived from a naturally occurring GPCR of Figure 1.

6. The isolated modified GPCR of claim 1, wherein the isolated,

modified GPCR is a Homo sapien GPCR.

7. The isolated modified GPCR of claim 1, wherein the isolated, modified GPCR is a Class A GPCR.

8. The isolated modified GPCR of claim 1, wherein the isolated, modified GPCR is a Class B GPCR.

9. The isolated modified GPCR of claim 1, wherein the isolated, modified GPCR is an orphan GPCR.

10. The isolated modified GPCR of claim 1, wherein the isolated, modified GPCR is derived from an odorant or taste GPCR.

11. The isolated modified GPCR of claim 1, wherein the isolated modified GPCR comprises a modified DRY motif selected from the group of Figure 2B.

12. An isolated modified arrestin polypeptide, wherein the isolated modified arrestin produces a constitutively desensitized GPCR when expressed in a cell.

13. An isolated modified GRK polypeptide, wherein the isolated

modified GRK produces a constitutively desensitized GPCR when expressed in a cell.

14. A polypeptide comprising SEQ ID NO: 1, 2, 3, 4, 5, or 6 and wherein the polypeptide when expressed in a cell binds arrestin in absence of agonist.

15. The polypeptide of claim 14, wherein the polypeptide further targets to an endocytic vesicle or endosome when the polypeptide is expressed in the cell.

16. A polypeptide of Figure 1, wherein the polypeptide comprises a modified DRY motif wherein the arginine of the DRY motif is any naturally occurring amino acid or synthetic amino acid except arginine.

17. A polypeptide selected from the group consisting of SEQ ID NO: 1 - 6, and wherein the polypeptide when expressed in a cell localized to endocytic vesicles or endosomes in absence of agonist.

18. A nucleic acid encoding an isolated modified GPCR or biologically active fragment thereof of claim 1.

19. A nucleic acid selected from the group consisting of SEQ ID Nos.: 7-12.

20. A nucleic acid encoding a polypeptide selected from the group consisting of SEQ ID Nos.:1 - 6.

21. A vector comprising a nucleic acid of claim 19.

22. A host cell comprising the expression vector of claim 21.

23. A method of identifying a compound which inhibits arrestin binding to a GPCR comprising:

a) preparing an isolated modified GPCR or biologically active fragment thereof which targets to an endocytic vesicle or endosome without agonist;

b) attaching the isolated modified GPCR or biologically active fragment thereof to a substrate;

c) exposing the isolated modified GPCR or biologically active fragment thereof to a candidate compound;

d) exposing the isolated modified GPCR or biologically active fragment thereof to an arrestin or biologically active fragment of arrestin; and

e) detecting whether interaction of the arrestin protein with the GPCR is decreased after exposure to the test compound, the decrease in interaction being an indication that the compound has activity.

24. A method of identifying compounds that interfere with agonist-independent localization of arrestin comprising:

(a) preparing a modified GPCR or biologically active fragment thereof;

(b) expressing the modified GPCR or biologically active fragment thereof in a cell that also expresses arrestin;

(c) exposing the cell to a candidate compound; and

(d) determining whether the candidate compound inhibits constitutive desensitization of the modified GPCR.

25. The method of claim 23, wherein the modified GPCR is a class A receptor.

26. The method of claim 23, wherein the modified GPCR is a class B receptor.

27. The method of claim 23, wherein the modified GPCR is an odorant or taste receptor.

28. The method of claim 23, wherein the modified GPCR is an orphan receptor.

29. The method of claim 24, wherein the modified GPCR is a class A receptor.

30. The method of claim 24, wherein the modified GPCR is a class B receptor.

31. The method of claim 24, wherein the modified GPCR is an odorant or taste receptor.

32. The method of claim 24, wherein the modified GPCR is an orphan receptor.

33. The method of claim 24 further comprising determining whether the candidate compound inhibits endosomal targeting of the modified GPCR.

34. The method of claim 24, wherein the arrestin is conjugated to a detectable molecule.

35. The method of claim 24, wherein the modified GPCR is conjugated to a detectable molecule.

36. The method of claim 34, wherein the detectable molecule is a radioisotope, an epitope tag, an affinity label, an enzyme, a fluorescent group, or a chemiluminescent group.

37. The method of claim 35, wherein the detectable molecule is a radioisotope, an epitope tag, an affinity label, an enzyme, a fluorescent group, or a chemiluminescent group.

38. A compound identified by the method of Claim 23.

39. A compound identified by the method of Claim 24.

40. A pharmaceutical composition for the treatment of a condition mediated by a GPCR in mammals comprising a therapeutically effective amount of a compound of Claim 38 and a pharmaceutically acceptable carrier.

41. A pharmaceutical composition for the treatment of a condition mediated by a GPCR in mammals comprising a therapeutically effective amount of a compound of Claim 39 and a pharmaceutically acceptable carrier.

42. A method of identifying a compound for GPCR antagonist or inverse agonist activity comprising:

a) preparing an isolated modified GPCR or biologically active fragment thereof which targets to an endosome or endocytic vesicle without agonist;

b) expressing the modified GPCR or biologically active fragment

thereof in a cell that also expresses a conjugate of arrestin and a detectable molecule;

c) exposing the cell a candidate compound;

d) detecting whether interaction of the arrestin protein with the GPCR is decreased after exposure to the test compound, the decrease in interaction being an indication that the compound has activity.

43. The method of claim 42, wherein the modified GPCR is an orphan receptor.

44. A non-human transgenic animal which expresses a modified GPCR of Figure 3.

45. The animal of claim 44, wherein the animal is a mouse

46. The animal of claim 44, wherein the non-human transgenic animal is a primate, a feline, a canine, a porcine, a bovine, a caprine, or an ovine.

47. A method of detecting a modified GPCR in a biological sample comprising assaying the biological sample with an antibody which recognizes and binds to the modified GPCR and determining whether the antibody bound the modified GPCR.

48. A method of detecting a nucleic acid of claim 19 in a biological sample comprising

(a) exposing the biological sample to a modified GPCR probe; and

(b) determining whether the modified GPCR probe bound the nucleic acid of the biological sample.

49. A composition comprising a substrate and one or more nucleic acids of claim 19 or fragments thereof which encode a motif of formula I, wherein formula I is a modified DRY motif.

50. A kit for detecting a modified GPCR in a biological sample comprising an antibody which recognizes and binds to the modified GPCR and reagents which detect the antibody that binds to the modified GPCR.

51. An isolated immunoglobulin which recognizes and binds to a modified GPCR.

52. The immunoglobulin of claim 51, wherein the immunoglobulin is a monoclonal antibody, a chimeric antibody, a human antibody, a bispecific antibody, a humanized antibody, a primatized antibody, or an antibody fragment.

53. The immunoglobulin of claim 51, wherein the antibody fragment is Fab, Fab', F(ab')2, F(v), and scFv.

54. A method of inhibiting constitutive desensitization of a GPCR by administering an effective amount of 2-ethyl-5,7-dimethyl-3-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-3H-Imidazo[4,5-b]pyridine to a patient in need thereof.

55. A method of inhibiting constitutive desensitization of a GPCR by administering an effective amount of phentolamine to a patient in need thereof.